Remarks

Further and favorable reconsideration is respectfully requested in view of the foregoing amendments and following remarks.

Thus, the disclosure in paragraph [0010] in the specification has been amended in response to the objection to the disclosure, thus rendering this objection moot.

Claims 1 and 2 have been cancelled.

Claim 3 has been rewritten in independent form, by incorporating the subject matter of original claims 1 and 2. In addition, amended claim 3 specifies the amount of active ingredient, based on the disclosure in paragraph [0018] of the specification.

Claims 4 and 5 have been amended, based on the disclosures in paragraphs [0015] and [0016], and Examples 1-6 which spray a solution of the active ingredient on partly pregelatinized starch.

Amended claim 4 refers to a fluidized bed granulation method, which corresponds to "a flow coater FBG-5" in each of Examples 1-6 in the specification. In this regard, Applicants are enclosing a catalogue showing that the "flow coater" is a type of fluidized bed granulation device.

The patentability of the presently claimed invention, after entry of the foregoing amendments, over the disclosure of the reference relied upon by the Examiner in rejecting the claims, will be apparent upon consideration of the following remarks.

Initially, Applicants respectfully submit that the rejection of claims 1, 2, 4 and 5 under 35 U.S.C. §102(b) as being anticipated by Ohyama et al. (EP '232) has been rendered moot in view of the claim amendments. This rejection does not include claim 3, and since claims 4 and 5 are now directly or indirectly dependent on claim 3, the rejection has been rendered moot as applied to these claims.

The rejection of claims 1-5 under 35 U.S.C. §103(a) as being unpatentable over Ohyama et al. is respectfully traversed.

With regard to amended claim 3, the Ohyama et al. reference discloses hydroxylpropylmethylcellulose 2910 (tradename: TC-5, manufactured by Shin-Etsu Chemical Co., Ltd., hereinafter, referred to as "the HPMC 2910 of the reference") which is used as a coating base for tablets including an active ingredient that is unstable to light. The added amount of the compound to tablets is a trace amount of 4.8%. Accordingly, it is clear that the HMPC

2910 in such a trace amount (4.8%) in the reference cannot function as a gel-forming material or a sustained-release base. Further, the HMPC 2910 of the reference is used as a "coating base" for tablets including an active ingredient that is unstable to light, and therefore it is not a problem for the material not to have any function for a sustained-release property.

Conversely, the HPMC 2910 (tradename: Metlose 60SH, manufactured by Shin-Etsu Chemical Co., Ltd., hereinafter, referred to as "the HPMC 2910 of the present invention") is used as a sustained-release base. Accordingly, a 2% aqueous solution of the HPMC 2910 of the present invention has a viscosity of 4000 cps (at 20°C), which is significantly higher than that of a common coating agent. Because of this high viscosity, the HPMC 2910 of present the invention has a property such that the material swells as it absorbs a solvent (for example, water) so that the colloid particles in the material are linked to one another to form a three-dimensional network structure, resulting in a less-fluid gel-like material (gel-forming material) . Furthermore, since the material is a key factor for imparting a sustained-release function, an abundance of the material is added to tablets, i.e. in an amount of 18 to 73 wt%.

As discussed above, the HPMC 2910 of the reference has quite a different purpose from the HPMC 2910 of the present invention, and is used in a very different amount with different viscosity. Accordingly, the subject matter of claim 3 is quite different from, and not suggested by, the Ohyama et al. reference.

With regard to amended claims 4 and 5, Ohyama et al. disclose direct compression tableting in Examples 1 to 3 and 5, a wet granulation compression method by means of agitation granulation in Example 4, and a wet granulation compression method by means of fluidized bed granulation in Examples 6 to 9.

It should be noted that, since the reference is not directed to manufacturing a sustained-release tablet, the excipients and the like used in the reference have no disadvantage for mixing and granulation properties.

Conversely, the sustained-release tablet of the present invention includes HPMC, serving as a tablet base, which is an essential component. HPMC which contains bulky granules has unsatisfactory fluidity. Furthermore, since HPMC can easily dissolve in water, granulation control thereof is quite difficult. This difficulty becomes more prominent as the added amount of HPMC in the tablet increases. Accordingly, it would be difficult to produce the tablet of the present invention containing a large amount of HPMC by the method disclosed in the reference.

However, the present invention can overcome the disadvantage in tablet production using HPMC, and can provide improved tablets in which a trace amount of active ingredient can be uniformly dispersed. This cannot be achieved by the method disclosed in the reference.

In the present invention, the main ingredient (KRP-197) and an additive with less change in formulation (such as partly pregelatinized starch) are allowed to serve as a core, on which the main ingredient is sprayed to give a granular composition with satisfactory uniformity of the main ingredient and fluidity. Then, HPMC and other additives are mixed thereto to give granules for making tablets with satisfactory uniformity of the main ingredient and fluidity. The granules are compressed into sustained-release tablets containing the main ingredient which is uniformly dispersed while contained in a trace amount of 1 mg or less, with the tablet showing well-controlled release of the active ingredient.

For these reasons, it is apparent that the subject matter of amended claims 4 and 5 is also not suggested by the Ohyama et al. reference.

Applicants recognize that claims 4 and 5 are drafted in product-by-process format. However, as a result of the process recited in these claims, the product itself is different from, and not suggested by, the Ohyama et al. reference, as will be discussed below.

<u>Product of Ohyama et al.</u>

1) In the preparation disclosed in the reference, the HPMC 2910 is used as a coating base for tablets including an active ingredient that is unstable to light.

2) A 2% aqueous solution of the HPMC 2910 of the reference has a viscosity of 3 to 15 cps (at 20°C), which is significantly low.

3) The amount of the HPMC 2910 of the reference added to tablets is a trace amount of 4.8wt%. Accordingly, it is clear that the HMPC 2910 in such a trace amount (4.8wt%), with a property of low viscosity, cannot function as a gel-forming material or a sustained-release base.

Applicants also note that the preparation disclosed in the reference dissolves immediately upon contact with digestive juice in the alimentary canal. Accordingly, the active ingredients contained therein also dissolve immediately and are absorbed into the body to sharply raise its blood level. In view of this, the preparation cannot maintain an appropriate blood level for a prolonged period of time, meaning that the preparation does not have any sustained-release function.

Further, the HMPC 2910 of the reference is used as a "coating base" for tablets including an active ingredient that is unstable to light, and therefore it is not a problem for the HPMC 2910 not to have any function for a sustained-release property.

Product of Present Invention

1) The HPMC 2910 of the present invention is used as a sustained-release base.

2) A 2% aqueous solution of the HPMC 2910 of the present invention has a viscosity of 4000 cps (at 20°C) , which is significantly higher than that of the HPMC 2910 of the reference.

3) An abundance of the HPMC 2910 of the present invention is added to tablets, i.e. , an amount of 18 to 73 wt%.

Because of the property of high viscosity, and the added amount (18 to 73 wt%), the HPMC 2910 of the present invention has a property such that the material swells as it absorbs a solvent (for example, water), so that the colloid particles in the material are linked to one another to form a three-dimensional network structure, resulting in a less-fluid gel-like material (gel-forming material).

The present invention is characterized in that the HPMC can form a gel-like material upon contact with digestive juices in the alimentary canal, due to the use of HPMC that has the above-mentioned properties and its amount, which have not been achieved by the HPMC of the reference and its amount. Upon contact with the digestive juice, the HPMC of the present invention forms a gel-like material to gradually release the active ingredients from the tablet. Accordingly, there is no sharp rise in blood level, but the present invention can maintain an appropriate blood level of active ingredient for a prolonged period of time.

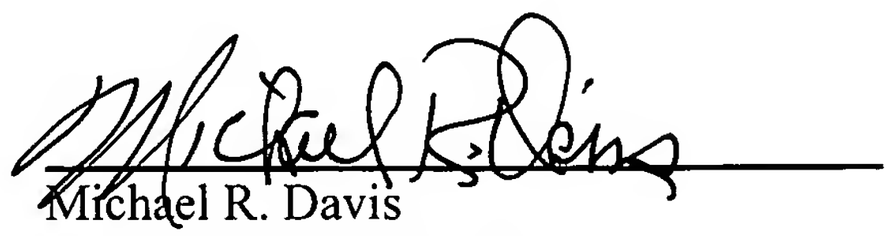
For these additional reasons, the presently claimed invention is considered to be clearly patentable over the Ohyama et al. reference.

The Examiner has provisionally rejected claims 1, 4 and 5 for obviousness-type double patenting as being unpatentable over claim 1 of Serial No. 11/795,792. This rejection has been rendered moot since claim 1 has been cancelled, and the rejection does not include claim 3 on which claims 4 and 5 are now directly or indirectly dependent.

Therefore, in view of the foregoing amendments and remarks, it is submitted that each of the grounds of rejection set forth by the Examiner has been overcome, and that the application is in condition for allowance. Such allowance is solicited.

Respectfully submitted,

Ryouichi HOSHINO et al.

By: 

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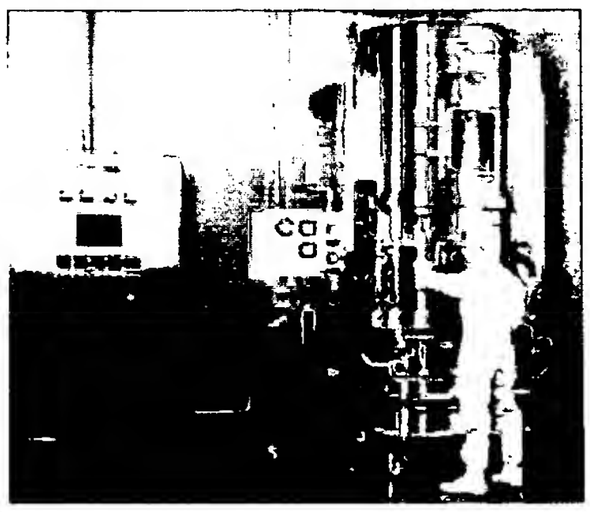
FLOW COATER

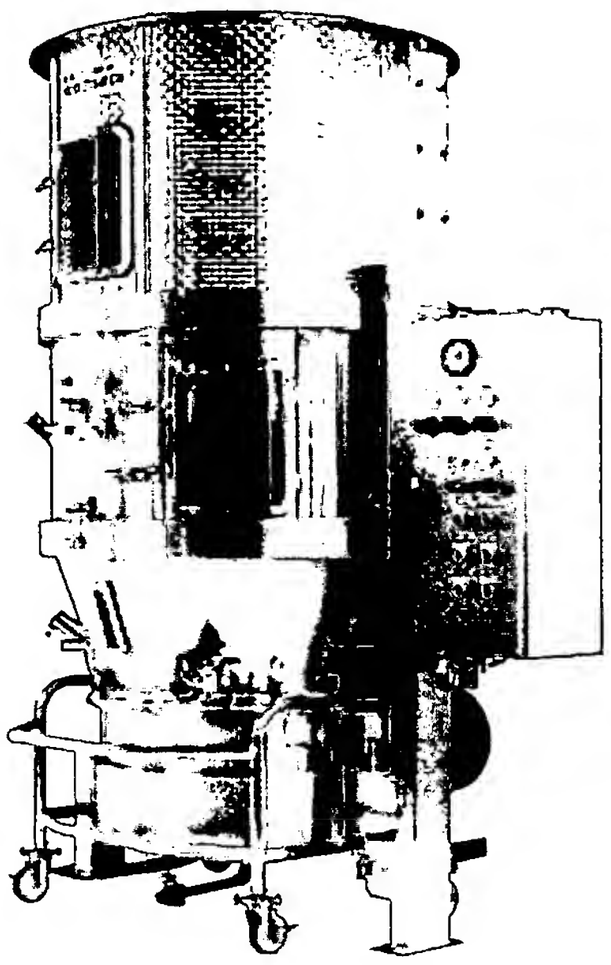
流動層造粒コーティング装置 “フローコーター”

流動層乾燥装置にスプレーシステムをドッキングした装置です。流動化(浮遊流動)された粉粒体に液体(バインダー液、コーティング液、抽出液など)をスプレーし、粉体の造粒や粒子のコーティングを行うことができます。溶解性、流動性に優れ、溶け易いポーラスな造粒物や、顆粒、ピルへのコーティングに適しています。また、一台の装置で混合～造粒～コーティング～乾燥といった複数の工程を連続して行うことができます。

●機種およびコンテナー容量
FL-MINI(1.0L)～
FLO-1000(2900L)11種類

〈FLOW COATER〉 is an unique fluidized bed equipment with solution spray system. Heated air is introduced through the bottom to fluidize the material bed (powders, pills) to which a binder solution,coating liquid or herbal extracts are sprayed to make granulation or coating. The features of FLOW COATER are as follows:1) short granulation time without loss in aroma potency, and 2) stable granulation with high porosity and flowability, rapid disintegration and dissolution in solvents, such as water.
●Eleven models are available from FL-MINI(1.0 liter) to FLO-1000 (2,900 liters).



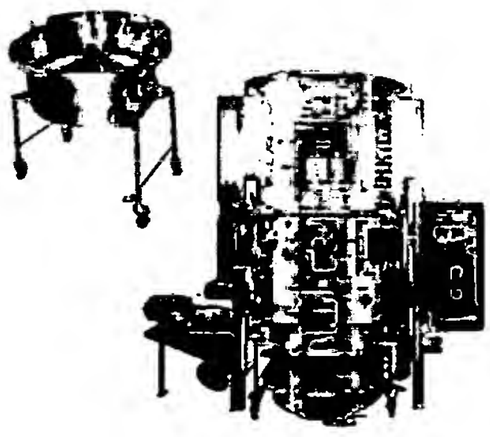


NFLO-120型

ROTOR CONTAINER

“ローターコンテナー”

流動層造粒コーティング装置<フローコーター>の標準コンテナーの代わりにこのローターコンテナーをワンタッチでセットすることにより、浮遊流動のほかに遠心転動、旋回流動の各機能を組み合わせて粒形、粒度、かさ密度等を自由にコントロールできます。



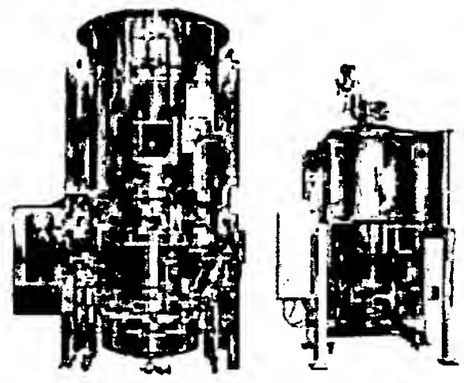
●機種およびコンテナー容量
FRC-5(15L)～
FRC-300(1000L)6種類

〈ROTOR CONTAINER〉 is inter-changeable with 〈FLOW COATER〉 standard container, and has a rotating disk with screen to give centrifugal and spiral functions. Attachment and removal are simple. It enables the precise granulation and uniform coating required in pharmaceutical use.
●Six models are avaliable from FRC-5 (15 liters) to FRC-300 (1,000 liters).

FLOW DRYER

流動層乾燥装置 “フロードライヤー”

安全性、生産性、サニタリー性、操作性など数多くの面で新規設計と改良を加えた新しい流動層乾燥装置です。静電気対策はもとより、種々の事態に対する安全性を考慮した設計になっております。バグフィルターの面積を拡大し、乾燥時間を短縮しました。



●機種およびコンテナー容量
NFOD-15(45L)～NFOD-300(1000L)7種類

“Safety”,“Productivity”,“Sanitation”,“Easy Operation”
〈FLOW DRYER〉 has been improved in all of these important points. The surface area of bag filter is increased to reduce drying time. Installation and removal are quick and easy. Many options are available to meet the various users' needs. Design and manufacturing standards conform to GMP.
●Seven models are available from NFOD-15 (45 liters) to NFOD-300 (1,000 liters).